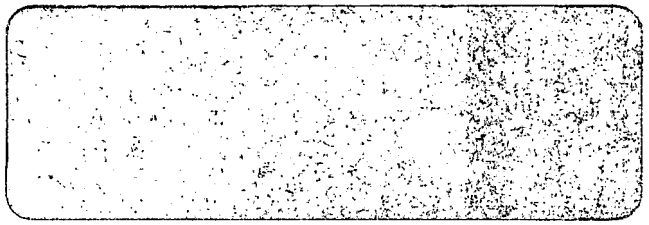
Organization TC1600 Bldg/Room REMSEN
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
If Undeliverable Return in Ten Days

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

AN EQUAL OPPORTUNITY EMPLOYER

Hasler
016H26521598
$01.560
10/26/2010
Mailed From 22206
US POSTAGE



RECEIVED
NOV 12 2010
TC 1600

REDD065+ 300712090 1709 04 11/08/10
FORWARD TIME EXP RTN TO SEND
:REDDY US THERAPEUTICS INC
200 SOMERSET CORPORATE BLVD FL 7
BRIDGEWATER NJ 08807-2862

RETURN TO SENDER

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,399	06/13/2005	Rajender Kumar Potlapally	DRF 33-010	3144

70554 7590 10/26/2010

Reddy Us Therapeutics, Inc
3065 Northwoods Circle
Norcross, GA 30071

EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
10/26/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,399	POTLAPALLY ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2-26-10 (RCE)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34 and 65-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34 and 65-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FIRST OFFICE ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-26-10 has been entered.

Claims 1-33, 35-37 and 58-64 are cancelled.

Claims 34 and 65-67 are pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 34, 66 and 67 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by **Chebiyyam et. al.** (WO'638).

Examples 39 and 40 describe the process of making potassium salt of Glitazone. The product is an off-white or white solid which could mean crystalline form since the term "solid"

includes crystals as well. Thus, Chebiyyam et. al. (WO'638) inherently encompasses the claimed crystalline form of Glitazone potassium salt.

2. Claims 34, 66 and 67 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by **Lohray et. al.** (WO'097). The salt of Example 41 is Form I which is the same as the instant potassium salt.

The reference of Lohray was withdrawn in the previous action. However, applicant's remark citing paragraph [0016] **admits** that Form I of WO'097 is the same as the form claimed in this application, see the following statement:

> **[0016]** The present invention also relates to a process for the preparation of 5-[4-[[3-Methyl-4-oxo-3,4-dihydroquinazolin-2-yl]methoxy]benzyl]thiazolidine-2,4-dione potassium salt **described** (*emphasis added*) in example 41 of our international application number PCT/US97/11522 (or Lohray et. al. WO 97/41097) which is designated as Form I.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 34 and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Chebiyyam et. al.** (WO'638—cited previously) in view of **Gu et. al.** ("Polymorph Screening: . . .", J. Pharm. Sci., 11/2001, Vol. 90, No. 11, pp. 1878 – 1890). Although claim 65 has been amended to recite specific solvents and a temperature range, said process would still yield the same Form I, and thus, would be obvious in view of Example 40 of WO'638 and the solvent comparison of Gu et. al.

The process in Example 40 still recites many steps as those recited in the instant claim 65 and Example 2 (pages 11-12) of the disclosure. That is, the disclosed process has the following analogous steps:

i. Glitazone base of step (i) was dissolved in xylene and methanol at about 80°C;

ii. potassium t-butoxide was added at 60-70°C;

iii. stirring at room temperature;

iv. obtaining the precipitate of form I of the instant Glitazone potassium salt.

The disclosed process of Example 40 differs from the claimed process by using the solvent of "xylene and methanol" and not "acetonitrile and xylene". However, selecting xylene/acetonitrile or xylene/methanol would be within the level of the skilled chemist to obtain

a desirable crystalline form because the choice of solvents depending on the following factors taught by Gu et. al. ("Polymorph Screening: . . .", J. Pharm. Sci., 11/2001, Vol. 90, No. 11):

i. A fast nucleation rate, or a "relatively high solubility but moderate solute-solvent interactions" (see page 1885, right column, the last 4 sentences);

ii. A weak hydrogen bonding propensity with a high solubility (to obtain a more stable polymorph) (see page 1887, left column, lines 6-8);

iii. A balance of solubility and the strength of the solvent-solute interactions (see page 1887, right column, the last three lines).

In the reference of Gu et. al., Table 1 lists acetonitrile as the solvent preferred over methanol for forming a stable polymorph since it has a fairly high solubility with less hydrogen bonding (or less van der Waals force), and a fast nucleation rate.

Thus, at the time of the invention, it would have been obvious to select the combination of "xylene/acetonitrile" to replace "xylene/methanol" as a solvent for the process described in Example 40 because such a solvent would been a "solvent of choice" to produce the claimed potassium salt in view of the combined teachings above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on Monday thru Friday (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

***

9-30-10

Notice of References Cited	Application/Control No. 10/507,399	Applicant(s)/Patent Under Reexamination POTLAPALLY ET AL.	
	Examiner TAMTHOM N. TRUONG	Art Unit 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	GU, C-H et. al., "Polymorph Screening: Influence of Solvents on the Rate of Solvent-Mediated Polymorphic Transformation", J. of Pharm. Sci., November 2001, Vol. 90, No. 1, pp. 1878 - 1890.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Polymorph Screening: Influence of Solvents on the Rate of Solvent-Mediated Polymorphic Transformation

CHONG-HUI GU,[1] VICTOR YOUNG JR.,[2] DAVID J.W. GRANT[1]

[1]Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Weaver-Densford Hall, 308 Harvard Street SE, Minneapolis, Minnesota 55455-0343

[2]Department of Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, Minnesota 55455

Received 17 October 2000; revised 7 May 2001; accepted 1 June 2001

ABSTRACT: Solvent-mediated polymorphic transformation is an efficient technique to obtain the most stable polymorph. The rate of solvent-mediated polymorphic transformation of sulfamerazine at 24°C in various solvents and solvent mixtures is controlled by the nucleation rate of the more stable Form II. The transformation rate is generally higher in the solvent giving a higher solubility and is low in the solvent giving a low solubility (8 mmol/L). In these solvents, because of a high interfacial energy, the metastable zone may be wider than the solubility difference between two polymorphs, such that the critical free energy barrier for nucleation cannot be overcome. In addition to the solubility, the strength of the solvent-solute interactions is also important in determining the transformation rate. For sulfamerazine, the transformation rate is lower in the solvent with a stronger hydrogen bond acceptor propensity. Because solubility is higher in the solvent with stronger hydrogen bond acceptor propensity, the balance of solubility and strength of hydrogen bonding interactions between the solute and solvent molecules determines the polymorphic transformation rate. Degree of agitation and temperature also change the polymorphic transformation rate by influencing the crystallization kinetics of the more stable polymorph. J Pharm Sci 90:1878–1890, 2001

Keywords: crystal growth; crystallization; hydrogen bonding; nucleation; polymorph; solubility; solvatochromic parameters; solvent-mediated transformation; sulfamerazine

INTRODUCTION

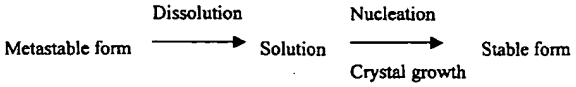
Polymorphism may be defined as the ability of a compound to exist in different crystalline forms in which the molecules have different arrangements and/or conformations in the crystal lattice.[1] Because different polymorphs exhibit significantly different pharmaceutically relevant properties, discovery, preparation, and characterization of polymorphs are essential preformulation steps in pharmaceutical research and development.[2] Usually, the most stable polymorphic form is preferred in a marketed formulation, because any other polymorphs are metastable and may therefore transform to the more stable form during storage. Such a phase change may cause formulation problems, for example, precipitation from solution, physical instability of solid dosage form, and changes in bioavailability. Overlooking the most stable polymorph may cause failure of a marketed product due to phase transformation during storage, for example, ritonavir.[3]

Currently, one of the most widely used methods for polymorph screening is recrystallization from different solvents.[4] However, according to Ostwald's rule of stages,[5] a metastable polymorph may often be obtained first during this process. An efficient method to discover the most stable

Chong-Hui Gu's present address is Bristol-Myers Squibb, 1 Squibb Drive, P.O. 191, New Brunswick, New Jersey 08903.

Correspondence to: D.J.W. Grant (Telephone: 1-612-624-3956; Fax: 1-612-626-2125; E-mail: grant001@tc.umn.edu)

Journal of Pharmaceutical Sciences, Vol. 90, 1878–1890 (2001)



Scheme 1. Processes of solvent-mediated polymorphic transformation.

polymorph is the technique of solvent-mediated polymorphic transformation.[6] In this technique, the less stable form is suspended in a saturated solution. The more stable form will then crystallize at the expense of dissolution of the less stable form, because the apparent solubility of this metastable form is higher than the solubility of the more stable form (Scheme 1). In addition to the preparation of the more stable polymorph, the technique of solvent-mediated transformation is also useful to examine the relative stability of polymorphs and to eliminate the less stable polymorph from a polymorphic mixture so as to ensure the phase purity. For these purposes, solvents that afford fast polymorphic transformation are preferred. On the other hand, to prepare the metastable polymorph by recrystallization from solution, solvents giving slow polymorphic transformation are preferred. Because the transformation rate in different solvents varies from minutes to years, an appropriate solvent should be chosen to either facilitate or retard the transformation. Currently, the choice of solvent is still by trial and error, which is time consuming. The purpose of this study is to illustrate the factors that govern the transformation rate, and thereby to provide guidelines to choose an appropriate solvent either to facilitate or to retard solvent-mediated polymorphic transformation. In addition, the influences of the degree of agitation and temperature on the polymorphic transformation rate in solution are also studied. Sulfamerazine (SMZ) was chosen as the model compound.

MATERIALS AND METHODS

Materials

SMZ (4-amino-N-[4-methyl-2-pyrimidinyl]benzenesulfonamide) was purchased from Sigma Co. (Lot # 47H0114, purity >99.9%). Polymorph I was prepared by recrystallization from isopropyl alcohol (IPA; 2-propanol). Polymorph II was prepared by suspending Form I in acetonitrile for 20 days.[7,8] The phase purity of each form thus prepared was found to be 100% by the suspension method.[8] All solvents used, including water, were HPLC grade. Residual water in the organic solvent was minimized by adding molecular sieves or anhydrous calcium sulfate (Drierite; Hammond, Xenia, OH). Solvent mixtures were prepared by mixing two solvents of predetermined volume.

Powder X-Ray Diffractometry (PXRD)

A PXRD diffractometer (D5005; Siemens, Germany) was used to identify the polymorphs and to determine the polymorphic compositions. The samples were exposed to Cu Kα radiation (45 kV and 40 mA) and were scanned from 14.5° to 16.5° 2θ at a step size of 0.01° and at 2 s per step. Preferred orientation was unlikely because the powder was very fine (particle size less than 50 μm). The peaks at 16.1° and 15.6° 2θ, corresponding to SMZ Form I and Form II, respectively, were chosen to determine the polymorphic composition by comparing the integrated peak areas (Figure 1), as described previously.[7] The peak areas of these two characteristic peaks were found to be identical for a 1:1 mixture of Polymorphs I and II. The detection limit was determined to be less than 1%, which enabled Polymorph II to be detected in the presence of Polymorph I with ease and with good reproducibility. The polymorphic composition was calculated by

$$\%\ \text{of Form II} = \frac{\text{peak area of the peak at } 15.6°2\theta}{\text{sum of peak areas of peaks at } 15.6° \text{ and at } 16.1°2\theta} \times 100\% \quad (1)$$

Solvent-Mediated Polymorphic Transformation

For SMZ, the transition temperature is 51–54°C. Polymorph I is metastable at 24°C but is more stable at higher temperatures. Polymorph I was suspended in its presaturated solution at 24°C. The ratio of suspended solid to solvent was 20 mg/mL. The suspension was shaken by a wrist-action shaker (Model 75; Burrell, Pittsburgh, PA) at approximately 300 strokes per minute. To study the transition from Polymorph I to Polymorph II at different temperatures and with different degrees of agitation, a shaking water bath (BT-47; Yamato Scientific Co., Ltd., Tokyo, Japan) was used to control the temperature and the degree of agitation. A portion of the suspension was withdrawn and filtered at designated times, and the polymorphic composition of the solid phase was determined by PXRD. Meanwhile, the

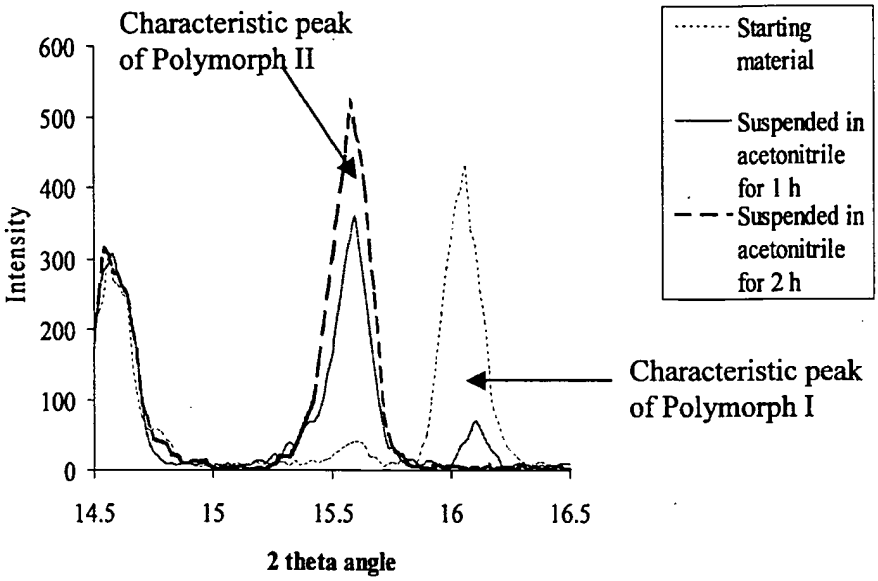


Figure 1. Powder X-ray diffraction patterns of mixtures of sulfamerazine Polymorphs I and II, suspended in acetonitrile after various times. The diffraction peaks used for quantification are shown by arrows.

concentration of SMZ in the solution during the transformation process was determined at $\lambda = 307$ nm with a spectrophotometer (DU 7400; Beckman, Irvine, CA).[9]

To determine the crystal growth rate of Form II, 90% of Form I and 10% of Form II were geometrically mixed (by geometric dilution) and were suspended in solutions, as stated above, to determine the polymorphic transformation rate. In the presence of 10% of Form II as seeds, the primary nucleation step in the transformation was bypassed. The polymorphic transformation rate thus determined corresponds to the crystal growth rate of the more stable Form II in solution.

Solubility

The solubility of SMZ Form II in various solvents and solvent mixtures was determined at 24°C. Excess solids were suspended in 10 mL of solvent and the suspension was equilibrated by shaking at 100 strokes/min in a shaking water bath (BT-47; Yamato Scientific Co., Ltd.). After 7 days, aliquots were drawn and the solvent was evaporated under vacuum. The solid residues were quantitatively dissolved in 0.1 M aqueous hydrochloric acid solution. The concentration of SMZ in the solution was determined by UV spectrophotometry,[9] as described under "Solvent-Mediated Polymorphic Transformation."

Recrystallization

Recrystallization of SMZ was performed in the following solvents: water, methanol, 2-propanol (IPA), acetonitrile, water-acetonitrile mixture (1:4, v/v), water-methanol mixture (1:4, v/v), and tetrohydrofuran. The saturated solutions were prepared both at 62°C and at 50°C and were cooled at a rate of 0.1°C/min. As soon as the solution became cloudy, the solution was filtered and the crystallized solid was examined by PXRD to determine the polymorphic form.

Scanning Electron Microscopy (SEM)

The morphology and particle size were analyzed by SEM (S-800; Hitachi, Tokyo, Japan) at an accelerating voltage of 10 kV. The samples were sputter-coated with platinum to a thickness of 50 Å.

Computer Software

The crystal structure of the SMZ polymorphs was downloaded from the Cambridge Structural Database and was visualized using Cerius2™ software (version 3.0; Molecular Simulations Inc., San Diego, CA). For statistical evaluations, the software employed was Statistix (version 7; Analytical Software Co., Tallahassee, FL).

RESULTS AND DISCUSSION

Solvent-Mediated Polymorphic Transformation

The solvent-mediated transformation consists of three parts: nucleation of the more stable polymorph, crystal growth of the more stable polymorph, and dissolution of the less stable polymorph (Scheme 1). Each step may be rate limiting. To determine whether the transformation rate is determined by the dissolution rate or by the crystallization rate (including nucleation and crystal growth), the concentration-time profile (Figure 2) of SMZ in solution during transformation was determined. From the concentration-time profile, the concentration remained constant at a value close to the solubility of Form I until more than 90% of suspended Form I had transformed to Form II. This phenomenon indicates that the crystallization rate of Form II is much slower than the dissolution rate of Form I, such that the loss of solute due to the crystallization of Form II was compensated immediately by the dissolution of Form I.[10] In all solvents used in this study, similar concentration-time profiles were observed. Therefore, the transformation rates in various solvents are controlled by the nucleation and crystal growth rate of Form II. During crystallization, the nucleation rate is generally slower than the crystal growth process.[11] In the polymorphic transformation of SMZ, the nucleation rate is slower than the crystal growth rate in all solvents except acetic acid, as shown in Table 1. Therefore, the polymorphic transformation rate of SMZ in various solvents is controlled by the nucleation rate of the more stable Polymorph II. The transformation rate varies widely in different solvents because the nucleation rate of SMZ Form II varies widely in different solvents. In the next section, the factors that govern the different nucleation rates in different solvents are discussed.

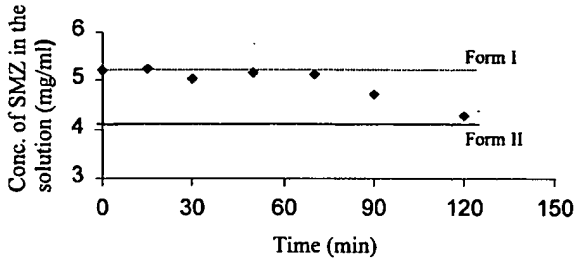


Figure 2. Representative concentration profile of solutions during polymorphic transformation. The dotted line represents the solubility of sulfamerazine Form I, while the full line represents the solubility of Form II.

Nucleation of Sulfamerazine Form II

It is virtually impossible to determine the true nucleation rate because nuclei are virtually undetectable by known techniques. However, it is generally accepted that the nucleation rate is inversely proportional to the induction time, which may be defined as the time lag for the first observable crystal to appear.[11] In this study, the time period in which Form II was first detectable in the suspension was taken as the induction time. Because the crystal growth rate is much faster than the nucleation rate (Table 1), we may ignore the lag time for the nuclei to grow into detectable crystals. Because the main purpose of this study is to compare the nucleation rate in different solvents, the relative nucleation rates were used to obtain the rank order of the actual nucleation rates, which are summarized in Figure 3. Generally, the nucleation rate is faster in the solvent that gives a higher solubility. Except in acetic acid, the nucleation rate becomes extremely slow in solvents in which the solubility is < 8 mmol/L. Form II was not detected in the suspension after 15 days. The influence of solubility on the nucleation rate can be explained by classical nucleation theory,[11–13] in which the nucleation rate for spherical particles is given by

$$J = N_0 \, v \exp\left(-\frac{\Delta G^* \Phi}{kT}\right) \tag{2}$$

where the critical free energy barrier for nucleation, ΔG^*, is given by

$$\Delta G^* = \frac{16\pi v^2 \gamma^3}{3(kT)^2 (\ln S)^2} \tag{3}$$

and where J is the number of nuclei formed per unit time per unit volume, N_0 is the number of solute molecules per unit volume, v is the frequency of molecular transport at the nucleus-liquid interface, Φ is the heterogeneous nucleation factor (in eq. 2), γ is the interfacial energy per unit area, v is the molecular volume of the solute, S is degree of supersaturation, which is equal to the activity ratio of the two polymorphs, T is the absolute temperature, and k is the Boltzmann constant (in eq. 3).

Because the degree of supersaturation is determined by the free energy difference, ΔG,

Table 1. Polymorphic Transformation Rate of Sulfamerazine in Various Solvents; and Solvent Solvatochromic Parameters, $\Sigma\alpha$, $\Sigma\beta$, and π^*

Solvent[a]	Induction Time (h)[b]	Time (h)[c] for 10% Form II to Convert to 75% Form II	Solubility (mmol/L)	$\Sigma\alpha^{d22}$	$\Sigma\beta^{e22}$	π^{*f20}
Acetonitrile	2	1	16.0	0.07	0.32	0.75
Nitromethane	72	54	15.1	0.06	0.31	0.85
Acetone	192	8	40.9	0.04	0.49	0.71
Tetrahydrofuran	144	24	70.2	0	0.56	0.58
Methanol	120	1	14.9	0.43	0.47	0.6
Ethanol	>360	—	7.91	0.37	0.48	0.54
2-Propanol	>360	—	1.28	0.33	0.56	0.48
Water	>360	72	1.05	0.82	0.35	1.09
Acetic acid	>360	>72	35.0	0.61	0.44	0.64
Dichloromethane	>360	—	4.12	0.1	0.05	0.82
Chloroform	>360	—	1.59	0.15	0.02	0.58
Water + acetonitrile 20%[g]	1	0.25	38.2	~0.42[h]	0.32–0.35[h]	—
Water + acetonitrile 80%[g]	>360	54	3.69	~0.7[h]	0.32–0.35[h]	—
Water + methanol 10%[g]	24	1.5	13.4	~0.45[h]	0.35–0.47[h]	—
Water + methanol 20%[g]	24	1.5	12.3	~0.45[h]	0.35–0.47[h]	—
Water + methanol 50%[g]	>360	7.5	4.43	~0.6[h]	0.35–0.47[h]	—
Methanol + dichloromethane 50%[g]	24	—	27.8	0.1–0.43[i]	0.05–0.47[i]	—
Water + acetone 33%[g]	72	—	16.6	0.04–0.82[i]	0.35–0.49[i]	—

[a]Italics mean that the nucleation rate in the solvent does not follow the rank order of solubility.
[b]Induction time is inversely proportional to the nucleation rate. The uncertainty of induction time is 0.25 h.
[c]This conversion time is inversely proportional to the crystal growth rate. The uncertainty of conversion time is 0.16 h.
[d]Hydrogen bond donor propensity.
[e]Hydrogen bond acceptor propensity.
[f]Dipolarity-polarizability.
[g]Volume percent (v/v) of solvent first mentioned.
[h]Based on reference.[35]
[i]Limits determined by the pure solvents, based on reference.[35]

between Forms I and II, it is identical in different solvents at the same temperature. The value of Φ ranges from 0 to 1 and is determined by the contact angle between the nuclei and the foreign solid surface in the solution.[11,14] In suspension, we may assume that the suspended particles of the metastable polymorph provide most of the foreign surface for nucleation. Therefore, the value of Φ is mainly determined by the affinity between the prenuclei of Form II and the suspended Form I, which should be identical in different solvents. In addition, because the concentration of the suspension is arranged to be identical in all experiments, the available surface for heterogeneous nucleation is similar in different solutions. The pre-exponential factor, $N_0\nu$, corresponds to the probability of intermolecular collision. The factor N_0 is equal to the concentration of the solute molecules in the solution and is therefore greater in the solvent giving the higher solubility. The factor υ in eq. 2 is mainly controlled by the degree of agitation, which is arranged to be constant in different experiments. The interfacial tension, γ, is inversely proportional to the logarithm of the solubility[15] according to the following equation:

$$\gamma = 0.414kT(c_S N_A)^{2/3}(\ln c_S - \ln c_{eq}) \qquad (4)$$

where c_S is equal to the ratio of the density of the solute to the molar mass of the solute, N_A is the Avogadro number, c_{eq} is the equilibrium solubility, and k and T have the meanings indicated above. Therefore, in the solvent that gives a higher solubility, N_0 is greater in eq. 2 and γ is smaller in eq. 4, while the other quantities remain identical, leading to a larger value of J in eq. 2, corresponding to a faster nucleation rate and transformation rate.

Because the system must overcome the critical nucleation energy barrier in order for nucleation to occur, a metastable zone exists between the two lines of steepest slope in Figure 4. Although the concentration of the solute in the solution is above

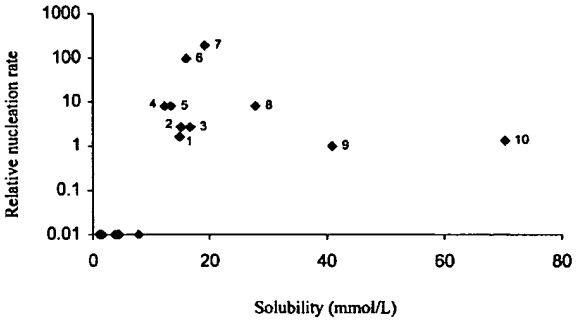


Figure 3. Relationship between the solubility and nucleation rate of sulfamerazine Form II in various solvents. Some corresponding solvents are: 1: methanol; 2: nitromethane; 3: 33% (v/v) water in acetone + water mixture; 4: 20% (v/v) water in methanol + water mixture; 5: 10% (v/v) water in methanol + water mixture; 6: acetonitrile; 7: 50% (v/v) water in acetonitrile + water mixture; 8: 50% (v/v) methanol in methanol + dichloromethane mixture; 9: acetone, 10: tetrahydrofuran.

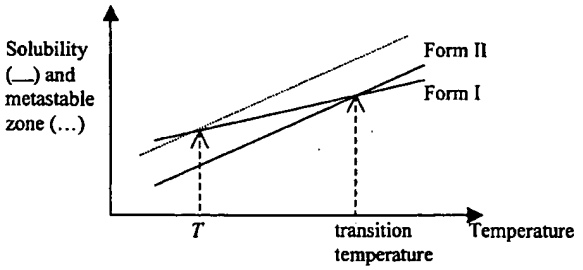


Figure 4. Solubility and upper limit of the metastable zone of an enantiotropic system. The dotted line represents the limit of the metastable zone, which has a width that increases with decreasing solubility. Between temperature, T, and the transition temperature, the transformation of sulfamerazine from Form I to Form II will not occur during a practical time range, because the solubility of Form I is within the metastable zone for nucleation of Form II. The lines are actually concave downwards.

the equilibrium solubility, within the metastable zone, the concentration is not high enough to overcome the critical free energy barrier, ΔG^*. In eq. 3, the metastable zone width for the polymorphic transformation process is determined by the interfacial tension, which increases as the solubility decreases (eq. 4). Therefore, the metastable zone width is wider in the solvent giving a lower solubility, corresponding to a higher free energy barrier, ΔG^*, for nucleation. In the case of polymorphic transformation, the degree of supersaturation, S, is a constant in various solvents. In the solvent giving a low solubility, when the metastable zone is wider than the solubility difference, or more accurately the activity difference, there is insufficient driving force to overcome the free energy barrier for nucleation, as illustrated in Figure 4. Therefore, the nucleation of Form II is less probable in those solvents giving lower solubilities, and the metastable Form I is kinetically more stable in those solvents.

Although solubility plays an important role in determining the nucleation rate of Form II, the nucleation rate is not always higher in the solvent giving a higher solubility, as shown in Table 1 and Figure 3. For example, the solubility is higher in acetone and tetrahydrofuran than in acetonitrile and nitromethane. However, the nucleation rate is faster in acetonitrile and nitromethane. Similarly, mixtures of methanol + water, containing 10% or 25% (v/v) water, give lower solubilities but higher nucleation rates than does pure methanol. These results suggest that solubility is not the only factor that determines the nucleation rate. Because most solutions are not ideal, solute-solute or solute-solvent interactions must be taken into consideration, which may significantly change the nucleation kinetics.[16]

The solvent-solute interaction may influence the nucleation and crystal growth rate in two ways. Firstly, the solute molecules in the solvent are associated with the solvent molecules, which are said to be solvated. During the nucleation and crystal growth step, desolvation of the solvated solute molecules must precede their integration into the crystal lattice. Secondly, the solvent molecules are adsorbed on the surface of a cluster of nuclei or a growing crystal surface. The incoming solute molecules must replace the solvent molecules in order to become integrated into the crystal lattice.[17] For both reasons, the stronger the solute-solvent interactions, the greater the retardation of nucleation and crystal growth, and the slower the polymorphic transformation rate in the solution. Furthermore, the recrystallization study showed that SMZ Form I always crystallizes first from the solvents, listed in the Materials and Methods section, if no seed of Form II is present. This result indicates that the growth unit of SMZ molecules, present in these solutions, favors the formation of Form I.[18,19] The stronger solvent-solute interaction may then stabilize those growth units and retard the crystallization of Form II.

To consider the effect of solute-solvent interactions, an effective collision factor, A, may be introduced into eq. 2. The factor, A, may be defined as the proportion of the collision of the solute molecules that effectively leads to the growth of nuclei. Clearly, A is smaller in the solvent giving stronger solvent-solute interactions.

Both the van der Waals force and hydrogen bonding contribute to the solute-solvent interactions. The strength of solute-solvent van der Waals interactions is determined by the dipolar-polarizability, π^*,[20] the values of which are listed in Table 1. The strength of hydrogen bonding interactions between the solvent and the solute is determined by both the hydrogen bond donor (HBD) propensity, $\Sigma\alpha$, or the hydrogen bond acceptor (HBA) propensity, $\Sigma\beta$.[21] The values of the HBD and HBA propensities of the solvents used in this study are listed in Table 1.[22]

On the other hand, solubility is correlated with the strength of the solvent-solute interactions. According to the linear free energy approach for predicting solubility,[23] the molar solubility of a solute compound in each member of a series of solvents can be expressed by the equation

$$\log s = a + b \cdot \delta^2 + c \cdot \Sigma\alpha + d \cdot \Sigma\beta + e \cdot \pi^* \quad (5)$$

where s is the molar solubility, δ is the solvent solubility parameter corresponding to the cohesive energy density, $\Sigma\alpha$, $\Sigma\beta$, and π^* are as defined above and a, b, c, d, and e are constants that depend on the given solute compound and that are determined by regression fitting. This approach has been summarized.[24] Using Statistix software, fitting the experimental solubility of SMZ Form II in pure solvents to eq. 5, assuming the reported solvent parameters,[20,22,25] gave the following relationship:

$$\log s = -4.46 - 0.00133\delta^2 + 1.63\pi^* + 2.90\Sigma\beta, \quad r^2 = 0.975 \quad (6)$$

The coefficient of $\Sigma\alpha$ in eq. 5 was found not to be significantly different from zero, which indicates that the HBD propensity of the solvent is not statistically important for determining the solubility of SMZ. Therefore, the HBD propensity term is omitted from the regression equation. The coefficients of HBA propensity and of dipolarity-polarizability are positive quantities, suggesting that the solubility of SMZ is higher in the solvent with greater HBA propensity and with greater dipolarity-polarizability. Therefore, the strength of solvent-solute interactions is greater in the solvent that gives higher solubility. Because the strength of the solute-solvent interactions and solubility exert opposite effects on the nucleation rate, the rate of solvent-mediated polymorphic transformation is determined by the balance of solubility and solute-solvent interactions.

To highlight which type of interaction plays the most important role in determining the nucleation rate, the nucleation rates in several solvents that do not follow the rank order of solubility are italicized in Table 1. In these solvents, a decrease in nucleation rate corresponds broadly to increases in solubility and HBA propensity (Figure 5). This result suggests that the HBA propensity of the solvent is important in determining both the nucleation rate and the solubility. No clear correlation was found between

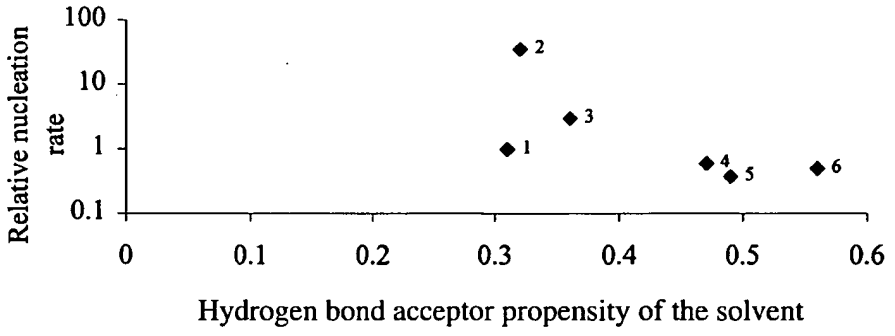


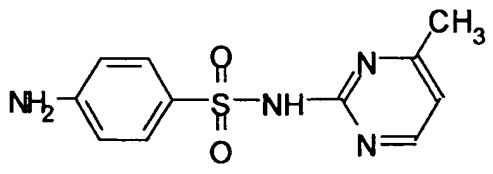
Figure 5. Relationship between the nucleation rate of sulfamerazine Form II and the hydrogen bond acceptor propensity (basicity) of the solvent. The corresponding solvents are: 1: nitromethane; 2: acetonitrile; 3: 20% (v/v) water in methanol + water mixture; 4: methanol; 5: acetone; 6: tetrahydrofuran.

either the HBD propensity of the solvent or the π^* factor of the solvent and the nucleation rate of Form II in these solvents. This phenomenon may be explained by the nature of the van der Waals force, which has a strength that is similar to that of the hydrogen bond but lacks the steric requirement, and exists universally in solutions. Hence, the change in van der Waals interactions may not be significant during the desolvation process, whereas the hydrogen bond has a strict steric requirement and mainly contributes to the desolvation energy.

The HBD propensity of the solvent is not important for the solubility or for the nucleation rate, while the HBA propensity of the solvent is important for both of these things. This result suggests that the primary solute-solvent interaction is that each solute molecule acts as a hydrogen bond donor while each solvent molecule acts as a hydrogen bond acceptor. SMZ is both an HBD and an HBA (Scheme 2). Using a computer program, Abraham et al. found that the $\Sigma\alpha$ value of SMZ is 0.8, and the $\Sigma\beta$ value of SMZ is 1.44.[26,27] This result suggests that SMZ possesses stronger HBA and HBD propensities than any of the solvents used in the study. However, the values of $\Sigma\alpha$ and $\Sigma\beta$ reflect the overall hydrogen bond propensity, which is given by the sum of the values for each functional group. Because of the relatively strong HBD propensity of the amino groups connected to the phenyl ring or to the pyrimidinyl ring, the solvent molecules cannot compete with the solute molecules as a donor to form a solvated molecule. However, the solvent may compete with the nitrogen atoms in the pyrimidine ring, which are relatively weak HBAs, to form the hydrogen bonds. Therefore, the stronger the HBA propensity of the solvent, the stronger the solute-solvent interaction, which may retard nucleation.

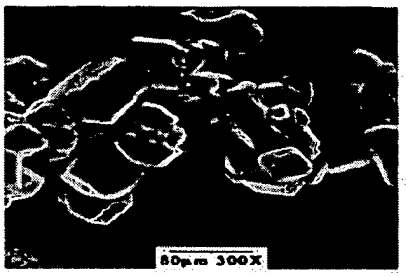
To further confirm the suggested solvent-solute interactions, we studied the morphology of SMZ Form II crystals grown from different solvents. Because the growth rate of a specific crystal surface will be retarded by a strong interaction between the solvent and this surface, the largest face of a crystal, which grows the slowest, undergoes the strongest interaction with the solvent. It is also generally accepted that the prenuclei possess a structure similar to that of the macroscopic crystals.[28] Therefore, the interaction between the prenuclei and the solvent will be similar to that between the macroscopic crystal surface and the solvent, which can be studied from the morphology. The morphology of SMZ Polymorph II grown in different solvents, determined by SEM, is given in Figure 6. The crystals of SMZ Form II that are grown in methanol, methanol + water mixture, methanol + dichloromethane mixture, acetone, and nitromethane are prism-shaped with a dominant (001) face. From the crystal structure of SMZ Form II,[29,30] the (001) face is found to contain the sulfonamide hydrogen atom attached to the pyrimidinyl ring, using Cerius2™ software (Figure 7). The solvent may bind to the sulfonamide hydrogen atom, –NH–, atom as an HBD to inhibit the growth of the (001) face. On the other hand, because the SMZ molecule is added to the (001) face through the interaction between the –NH– group (Scheme 2) and the nitrogen atom on the pyrimidinyl ring,[30] the solvent may bind to the –NH group in solution as an HBA to inhibit the growth of the (001) face. Unlike the morphology of the crystals grown in methanol, the morphology of those grown in acetonitrile shows more minor faces of {111} form, such as $(\bar{1}1\bar{1})$, $(11\bar{1})$, and (111). This result further suggests that the solvent-crystal surface interactions in acetonitrile are weaker, such that the growth rate of the (001) face is not slow enough to exclude the {111} faces. Nitromethane possesses solvatochromic parameters similar to those of acetonitrile, but the morphology of SMZ Form II grown in these two solvents is different. This result may be attributed to the fact that nitromethane can undergo tautomerism (Scheme 3), and then behaves like methanol, while acetonitrile cannot do so.

We may conclude that the nucleation rate is a function of a balance of solubility and strength of solvent-solute interaction. Although, in general, the nucleation rate is higher in the solvent that gives a higher solubility, the stronger solute-solvent interactions in those solvents may retard nucleation in a fashion similar to the effect of soluble additives. Therefore, the fastest nucleation rate may be observed in the solvent that gives a relatively high solubility but moderate solute-solvent interactions.

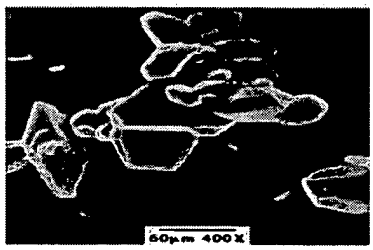


Scheme 2. Molecular structure of sulfamerazine.

From acetonitrile



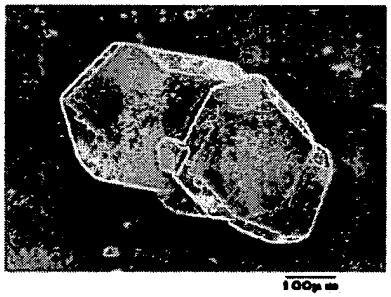
From 20% (v/v) water in acetonitrile + water mixture



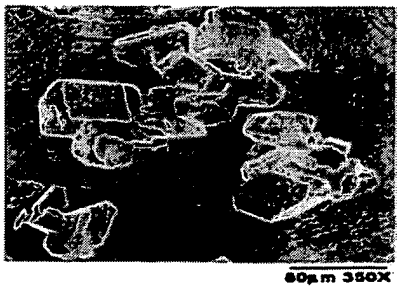
From methanol

From 20% (v/v) water in methanol + water mixture

From 50% (v/v) methanol in methanol + dichloromethane mixture



From nitromethane



From acetone

Figure 6. Morphology of sulfamerazine Form II from various solvents.

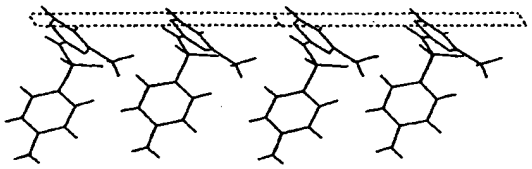


Figure 7. Molecular arrangement of sulfamerazine molecules at the (001) face of Form II.[29]

Polymorphic Transformation Rates in Mixed Solvents

As discussed above, a solvent with a strong hydrogen bonding propensity but giving a low solubility should be chosen to retard a solvent-mediated polymorphic transformation, for example to crystallize a metastable polymorph. On the other hand, a solvent with a weak hydrogen bonding propensity but giving a high solubility is preferred to crystallize a more stable polymorph. Because the solubility and the strength of the solute-solvent interactions are correlated in most pure solvents, it may be difficult to choose a suitable pure solvent for polymorph screening. However, solvent mixtures may be prepared to obtain the desirable properties for polymorph screening.[31,32] In acetonitrile + water mixtures, the solubility and the nucleation rate of Form II increase to a maximum at 20% (v/v) water (Figure 8). This result may be explained by the increase in solubility in acetonitrile + water mixtures. On the other hand, the HBA propensity of the solvent mixture is identical to that of the pure solvent, because the HBA propensities of water and acetonitrile are similar (Table 1). In methanol-water mixtures, although the solubility decreases with increasing proportion of water in the mixture, the HBD and HBA propensities decrease with the increasing proportion of water in the mixed solvent. The overall effect is that a maximum nucleation rate is achieved at 10–20% (v/v) water in methanol + water mixtures (Figure 9). This result may be explained by the dramatic decrease in the HBA propensity of the solvent with addition of methanol.[32] In addition, the nucleation rate is faster in 50% (v/v) methanol in methanol + dichloromethane mixtures and in

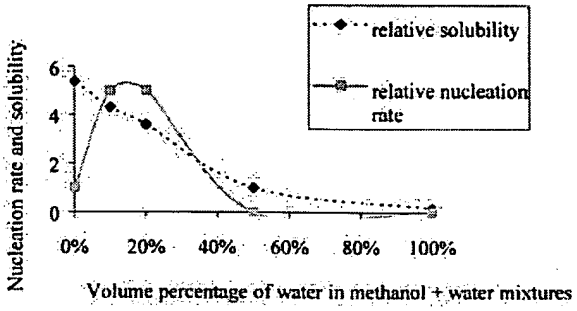
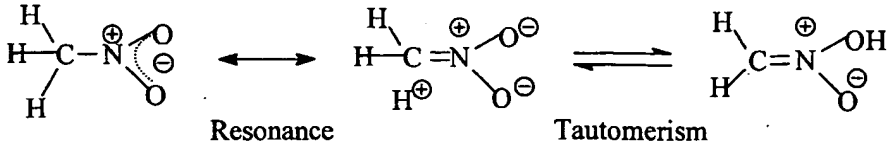


Figure 8. Solubility and nucleation rate of SMZ Form II in methanol + water mixtures, relative to the corresponding quantity in the pure solvent.

33% (v/v) water in water + acetone mixtures than in the pure solvents. The HBA propensity of acetone and methanol may be diluted by dichloromethane or water, which have weak HBA propensity. On the other hand, although the HBA propensity is decreased by dilution, the solubility may be increased due to the reduction of the cohesive energy density of the solvent; such an example is the solubility of Form II in 50% (v/v) methanol in the methanol + dichloromethane mixture (Table 1). The nucleation rate in the methanol + dichloromethane mixture is therefore faster than that in the pure solvents, because of the higher solubility and weaker solute-solvent interactions.

Crystal Growth Rate

The crystal growth rates of SMZ Form II in different solvents were determined by monitoring the polymorphic composition of suspension, which initially consisted of 10% Form II and 90% Form I of SMZ. The relationship between the relative nucleation rate and the relative crystal growth rate in different solvents is summarized in Figure 10. The crystal growth rate is generally higher in a solvent with a faster nucleation rate, although they are not correlated exactly and monotonically. This phenomenon is attributed to the fact that the balance of solubility and the strength of the solvent-solute interactions deter-



Scheme 3. Resonance and tautomerism of nitromethane molecules.

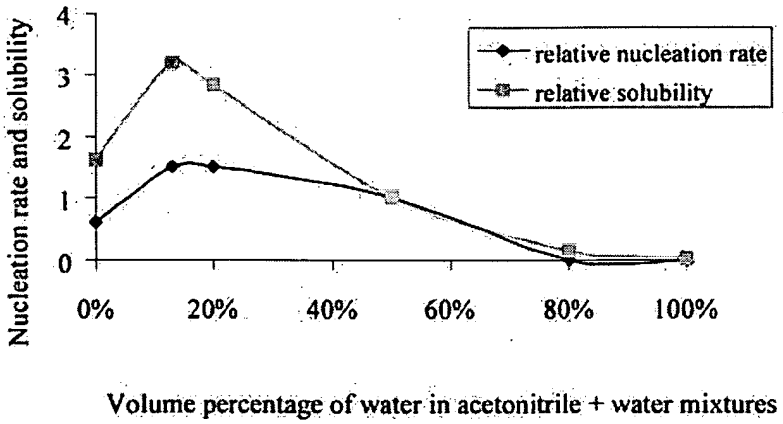


Figure 9. Solubility and nucleation rate of sulfamerazine Form II in acetonitrile + water mixtures, relative to the corresponding quantity for the pure solvent.

mines the crystal growth rate. The roughness of a growing surface increases with increasing solubility.[33] A rough surface contains more kink sites, at which the growth units are incorporated, than a smooth surface. Therefore, at the same degree of supersaturation, the crystal growth rate is faster at a rougher surface. However, the stronger solute-solvent interactions in the solvent that gives a higher solubility will more effectively retard the desolvation step, which is an essential stage during crystal growth.[34] Therefore, the crystal growth rate reaches a maximum in a solvent with moderate strength of solute-solvent interactions but giving a high solubility.

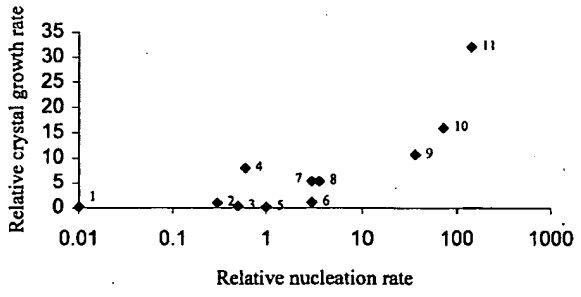


Figure 10. Relationship between the nucleation rate and the crystal growth rate of sulfamerazine Form II in various solvents. The solvents corresponding to each point are: 1: water; 2: acetone; 3: tetrahydrofuran; 4: methanol; 5: nitromethane; 6: 20% (v/v) water in methanol + water mixture; 7: 10% (v/v) water in methanol + water mixture; 8: 50% (v/v) methanol in methanol + dichloromethane mixture; 9: acetonitrile; 10: 50% (v/v) water in acetonitrile + water mixture; 11: 20% (v/v) water in acetonitrile + water mixture.

The rank order of crystal growth rate does not exactly follow the rank order of nucleation rate. This result indicates differences between the relative importance of solubility and solvent-solute interactions in determining the nucleation rate and crystal growth rate. In addition, the growth mechanism in different solvents may differ, that is, the crystal growth rate may be determined by the integration of the solute molecules into the growing steps or by the diffusion of the solute molecules in the bulk solution or at the interface.[6,11,33] If the crystal growth rate in some solvents is determined by the diffusion rate of the solute in the bulk solution, the viscosity of the solvent will also affect the growth rate. Because nucleation is slower than crystal growth in most crystallization processes, we may primarily consider the factors that influence the nucleation rate to choose the appropriate solvent for screening polymorphs by solvent-mediated transformation.

Influence of Temperature and Degree of Agitation on the Rate of Polymorphic Transformation

The influence of temperature and degree of agitation on the polymorphic transformation rate was studied in the transformation from Form I of SMZ to Form II in acetonitrile. The results are summarized in Table 2. The crystal growth rate is identical when the degree of agitation is increased from 100 to 300 stroke/min. This result indicates that the crystal growth rate in acetonitrile is controlled by the rate of integration of the solute molecules into growing crystals rather than by the diffusion rate of the solute molecules in the

Table 2. Relative Rates of Nucleation and Crystal Growth for Sulfamerazine Polymorph II in Acetonitrile at Different Temperatures and Degrees of Agitation

	24°C, 300 Stroke/Min	24°C, 100 Stroke/Min	30°C, 100 Stroke/Min	50°C, 100 Stroke/Min
Relative nucleation rate	1	0.5	0.0625	0
Relative crystal growth rate	1	1	0.62	0.17

bulk solution.[11,33] However, the nucleation rate is faster at a higher degree of agitation. This result may be explained by the increase in the rate of transport of solute molecules at a higher degree of agitation (eq. 2), which will then increase the nucleation rate.[11]

At different temperatures, the free energy difference between two polymorphs is different. For SMZ, below the transition temperature, 51–54°C, the modulus of the free energy difference between Polymorph I and II decreases as the temperature increases. Therefore, the degree of supersaturation at 50°C or at 30°C is smaller than that at 24°C. Although the molecular motion is higher and the interfacial energy is lower at a higher temperature, which may facilitate nucleation and crystal growth, the degree of supersaturation plays a decisive role in the rates of nucleation and crystal growth. Therefore, the rates of nucleation and crystal growth are both slower at a higher temperature, 30°C, than at a lower temperature, 24°C. At 50°C, the solubility difference between the two polymorphs becomes too small to provide a sufficient driving force for nucleation to occur.

CONCLUSION

The rate of solvent-mediated polymorphic transformation of SMZ is controlled by the nucleation rate. The transformation rate is determined by a balance of solubility and strength of the solvent-solute interactions, mainly the hydrogen bonding interactions. To facilitate polymorphic transformation for the crystallization of the more stable polymorph, the metastable polymorph may be suspended in a solvent that gives a high solubility but moderate solvent-solute interactions. For crystallization of the metastable polymorphs, a solvent that gives a low solubility should be chosen to retard polymorphic transformation in solution. Solvent mixtures may provide some desirable properties for polymorph screening. Both the temperature and degree of agitation influence the polymorphic transformation rate in solutions. The change in degree of agitation may increase the nucleation rate and hence facilitate the transformation. Temperature mainly affects the degree of supersaturation because of its influence on the free energy difference between polymorphs. The decrease in the degree of supersaturation due to a change in temperature lowers the rates of nucleation and crystal growth and hence lowers the rate of polymorphic transformation.

ACKNOWLEDGMENTS

We thank Professor Michael Abraham, Department of Chemistry, University College London, for kindly calculating the hydrogen bond acceptor and donor propensities of sulfamerazine. We also thank Bristol-Myers Squibb for kindly providing financial support and the Supercomputing Institute of the University of Minnesota for financially supporting our use of the Medicinal Chemistry/Supercomputing Institute Visualization-Workstation Laboratory.

REFERENCES

1. Grant DJW. 1999. Theory and origin of polymorphism. In: Brittain HG, editor. Polymorphism in Pharmaceutical Solids. New York: Marcel Dekker. p 1–33.
2. Haleblian J, McCrone W. 1969. Pharmaceutical applications of polymorphism. J Pharm Sci 58:911–929.
3. Abbott Laboratories. 1998. Letter to health care provider http://wwwfdagov/medwatch/safety/1998/novir.htm.
4. Guillory J. 1999. Generation of polymorphs, hydrates, solvates, and amorphous solids. In: Brittain HG, editor. Polymorphism in Pharmaceutical Solids. New York: Marcel Dekker. p 183–226.
5. Ostwald W. 1897. Studien Über Die Bildung und Umwandlung Fester Körper. Z Physik Chem 22: 289–330.

6. Rodriguez-Hornedo N, Murphy D. 1999. Significance of controlling crystallization mechanisms and kinetics in pharmaceutical systems. J Pharm Sci 88:651–660.
7. Zhang G. 1998. Influence of Solvents on Properties, Structures, and Crystallization of Pharmaceutical Solids. PhD Thesis. Minneapolis: University of Minnesota. p 70–122.
8. Gu C, Grant DJW. 2001. Estimating thermodynamic stability relationships of polymorphs and solvates from heats of solution and either solubilities or dissolution rates. J Pharm Sci 90:1277–1287.
9. Woolfender RDG. 1977. Sulfamerazine. In: Florey K, editor. Analytical Profiles of Drug Substances, Vol. 6. New York: Academic Press. p 515–517.
10. Cardew PT, Davey RJ. 1982. The kinetics of solvent-mediated phase transformations. Proc R Soc Lond A 398:415–428.
11. Mullin JW. 1993. Crystallization. 3 ed. London: Butterworth-Heinemann.
12. Gibbs J. 1948. Collected Works, Vol. I, Thermodynamics: New Haven: Yale University Press.
13. Volmer M. 1939. Kinetic der Phasenbildung, Steinkopff. Leipzig.
14. Fletcher N. 1963. Nucleation by crystalline particles. J Chem Phys 31:237–240.
15. Mersmann S. 1990. Calculation of interfacial tensions. J Cryst Growth 102:841–847.
16. Davey R, Milisavljevic B, Bourne JR. 1998. Solvent interactions at crystal surfaces: The kinetic story of α-resorcinol. J Phys Chem 92:2032–2036.
17. Khoshkhoo S, Anwar J. 1993. Crystallization of polymorphs—the effect of solvent. J Phys D: Appl Phys 26:B90–B93.
18. Blagden N, Davey RJ, Lieberman HF, Williams L, Payne R, Roberts R, Rowe R, Docherty R. 1998. Crystal chemistry and solvent polymorphic systems—sulfathiazole. J Chem Soc Faraday Trans 94:1035–1044.
19. Gidalevitz D, Feidenhansl R, Matlis S, Smilgies DM, Christensen MJ, Leiserowitz L. 1997. Monitoring in situ growth and dissolution of molecular crystals: Towards determination of the growth unit. Angew Chem Int Ed Engl 36:955–959.
20. Marcus Y. 1993. The properties of organic liquids that are relevant to their use as solvating solvents. Chem Soc Rev 73–83.
21. Taft R, Gurka D, Joris L, Schleyer P, von R, Rakshys JW. 1969. Studies of hydrogen-bonded complex formation with p-fluorophenol. V. Linear free energy relationships with OH reference acids. J Am Chem Soc 91:4801–4808.
22. Abraham M. 1993. Scales of solute hydrogen-bonding: Their construction and application to physicochemical and biochemical processes. Chem Soc Rev 73–83.
23. Taft R, Abraham MH, Doherty RM, Kamlet MJ. 1985. The molecular properties governing solubilities of organic nonelectrolytes in water. Nature 313:384–386.
24. Higuchi T, Grant DJW. 1990. Solubility Behavior of Organic Compounds. In: Saunders WJ, editor. Techniques of Chemistry. New York: John Wiley & Sons. p 22–36.
25. Riddick J, Bunger WB, Sakano TK. 1986. Organic Solvents: Physical Properties and Methods of Purification. Vol. 4. New York: John Wiley & Sons.
26. Platts J, Butina D, Abraham MH, Hersey A. 1999. Estimation of molecular LFER descriptors using a group contribution approach. J Chem Inf Comput Sci 39:835–845.
27. Abraham M. Personal communication.
28. Weissbuch I, Porovitz-Biro R, Lahav M, Leiserowitz L. 1995. Understanding and control of nucleation, growth, habit, dissolution and structure of two- and three-dimensional crystals using 'tailor-made' auxiliaries. Acta Cryst B51:115–148.
29. Acharya K, Kuchela K. 1982. Crystal structure of sulfamerazine. J Crystallogr Spectrosc Res 12:369–376.
30. Caira M, Mohamed R. 1992. Positive identification of two orthorhombic polymorphs of sulfamerazine ($C_{11}H_{12}N_4O_2S$), their thermal analyses and structure comparison. Acta Cryst B48:492–498.
31. Waghorne W. 1993. Thermodynamic of solvation in mixed solvents. Chem Soc Rev 285–292.
32. Tan L, Carr P. 1988. Study of retention in reversed-phase liquid chromatography using linear solvation energy relationships II. The mobile phase. J Chromatogr 799:1–19.
33. Nyvlt J, Sohnel O, Matuchova M, Broul M. 1985. The kinetics of industrial crystallization. Amsterdam: Elsevier, p 149–183.
34. Davey R. 1982. Solvent Effects in Crystallization processes. In: Kaldis E, editor. Current topics in Materials Science. Amsterdam: North-Holland Publishing Co., pp. 429–479.
35. Carr PW, Doherty RM, Kamlet MJ, Taft RW, Melander W, Horvath C. 1986. Study of temperature and mobile-phase effects in reversed-phase high-performance liquid chromatography be the use of the solvatochromic comparison method. Anal Chem 58:2674–2680.